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**WO 01/52897 A2**

(54) Title: THERAPEUTIC ANTI-INFLAMMATORY AND ANALGESIC COMPOSITION CONTAINING SELECTIVE COX-2 INHIBITOR DRUGS FOR USE TRANSDERMALLY AND A PROCESS FOR THE MANUFACTURE THEREOF

(57) Abstract: A therapeutic anti-inflammatory and analgesic composition for topical/transdermal use which comprises: Selective Cox-2 inhibitor drugs from 0.1% to 40% w/w and percutaneous absorption enhancing vehicle/base from 60% to 99.9% w/w. Optionally Gelling agent/thickening agent (0% to 60% w/w) surfactant (0% to 20% w/w). Neutralizing agent/pH adjusting agent (0% to 5% w/w) may be added to the said composition.

Attorney Docket No. 01371/2/US

Inventor: Inoo et al.

Application No. 10/683,623

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# THERAPEUTIC ANTI-INFLAMMATORY AND ANALGESIC COMPOSITION CONTAINING SELECTIVE COX-2 INHIBITOR DRUGS FOR USE TRANSDERMALLY AND A PROCESS FOR THE MANUFACTURE THEREOF

## TECHNICAL FIELD

This invention relates to novel therapeutic anti-inflammatory and analgesic pharmaceutical compositions containing Selective COX- 2 inhibitors drugs for use transdermally and a process for the manufacture thereof.

## BACKGROUND OF THE INVENTION

For a drug to be absorbed transdermally, it has to travel through various layers of the skin before reaching the site of action.

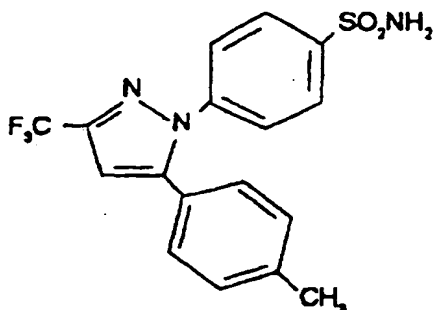
The layers of the skin are different in nature-some are hydrophilic while some are lipophilic (Montagna W. Parrakhal PF: The structure and Function of the skin, 3<sup>rd</sup> ed. Academic press, New York, 1974). Accordingly, any drug which is used transdermally must possess both hydrophilic and lipophilic properties. COX- 2 inhibitor drugs such as Celecoxib and Rofecoxib are a highly hydrophobic drugs and consequently they are considered poor candidate for transdermal absorption. When applied to the skin, these are absorbed in very minute quantities or not absorbed at all.

A transdermal route for administration of anti-inflammatory agents offers various advantages over the oral route such as lower dosage, less toxicity/side effects, no G I irritation, no dose dumping in the body and it is more site specific (Chien YW: Novel Drug Delivery System, Marcel Dekker, New York, 1982).

The identification of two cyclooxygenase (COX) enzymes has been a tremendous advance in understanding the role of prostaglandins in inflammation and the actions of nonsteroidal anti-inflammatory drugs (NSAIDs.) COX-1 activity appears to be related to "constitutive" or "house-keeping" functions in the gastric mucosa, kidney and platelets. COX-2 activity is "inducible" and generally occurs in response to a specific stimulus to enhance inflammatory actions. Current NSAIDs inhibit both COX-1 and COX-2, although the clinical benefit of NSAIDs appears to be associated with inhibition of COX-2 activity. The inhibition of COX-1 activity by NSAIDs is related to adverse side effects in general, particularly gastrointestinal toxicity. Recently, COX-2 selective inhibitors have been developed. Current data would suggest that by inhibiting COX-2 action, these agents may have efficacy similar to that of standard NSAIDs and that by not inhibiting COX-1 activity, they may have less toxicity than standard NSAIDs. Thus, these actions indicate that COX-2 selective inhibitors will have similar clinical efficacy to the traditional NSAIDs with fewer adverse side effects.

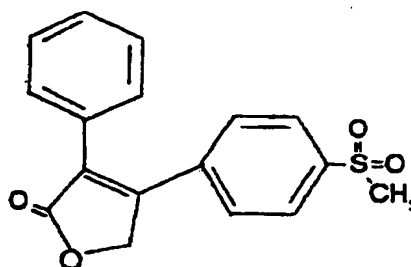
Celecoxib is a known selective COX-2 inhibitor having analgesic and anti-inflammatory activity, but which has the drawback of having unfavourable chemical-physical characteristics; the main obstacle to the use of celecoxib in topical formulation is in fact its insolubility in water and, on the other hand, its poor solubility in the solvents/raw materials usually employed in such formulation.

The chemical structure of Celecoxib and Rofecoxib are given hereinbelow alongwith their chemical names:-



**Celecoxib**

Celecoxib:- p[5-p-Tolyl-3-(trifluoromethyl) pyrazol-1-yl] benzenesulfonamide.



**Rofecoxib**

Rofecoxib:- 4-[4-(methyl sulphonyl) phenyl]-3-phenyl-2(5H)-furanone.

In the Patent Application PCT Publication No. PCT/US94/12720 Celecoxib is disclosed. However, no transdermal composition of this Drug is disclosed.

It is an object of the present invention to provide a therapeutic composition containing COX-2 inhibitor in combination with other compounds which alter the hydrophobic property of Nimesulide and a process for the manufacture thereof thus making it possible for the composition to be used for direct application on the skin for the treatment of inflammation through transdermal absorption.

It is a further object of the present invention to provide a novel therapeutic composition containing COX-2 invention in combination with other compounds which alter the physico-chemical property of COX-2.

## SUMMARY OF THE INVENTION

The present invention provides a Novel Therapeutic Anti-inflammatory and Analgesic Pharmaceutical composition for topical use which comprises :

1. Selective COX-2 inhibitor drugs : 0.1% to 40% w/w.
2. Percutaneous absorption : 60% to 99.9% w/w  
enhancing vehicle base.

The said Percutaneous enhancing vehicle base comprises :

1. Percutaneous enhancer : 0.5% to 60% w/w
2. Surfactant : 0.0% to 20 % w/w
3. Gelling agent/Thickening agent : 0.0% to 60% w/w
4. One or more vehicle/base : 2% to 98% w/w.

Preferably the percutaneous enhancing base comprises :

1. Percutaneous enhancer : 6% to 15% w/w
2. Surfactant : 0.5% to 12% w/w
3. Gelling agent/Thickening agent : 0.5% to 19% w/w
4. One or more vehicle/base : 5% to 60% w/w.

One or more percutaneous enhancers can be used in compositions according to this invention. One or more surfactants can be used in compositions according to this invention. One or more gelling agents/thickening agents can be used in compositions according to this invention.

Besides the above disclosed ingredients the composition for topical use also comprises a neutralizing agent/pH adjusting agent such as herein described in the range of 0.0% to 5.0%.

## DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, it has been found that it is possible to deliver a highly hydrophobic drugs such as COX-2 inhibitor drugs to the site of action through a transdermal route. The present invention involves the process of incorporation of COX-2 inhibitor drugs in a formulation which can transport the drug through the skin barriers, in intact condition to the site of action.

Preferably the percutaneous enhancing base comprises :

1. Percutaneous enhancer : 6% to 15% w/w
2. Surfactant : 0.5% to 12% w/w
3. Gelling agent/Thickening agent : 0.5% to 19% w/w
4. One or more vehicle/base : 5% to 60% w/w.

Preferably the COX-2 inhibitor drugs are in the range of 0.2% to 20% w/w. More preferably the composition for topical use also comprises a Neutralising agent/ph adjusting agent as herein described in the range of 0.0% to 2.0%.

The novel Therapeutic Anti-Inflammatory and Analgesic Composition for topical use according to the present invention, is prepared by the process which comprises the following steps :

- (a) 0.5% to 60% w/w of a Percutaneous enhancer, as herein described, is mixed with 2.0% to 98% w/w of one or more Vehicle or base, as herein described, in a container by stirring and to the mixture obtained 0.1% to 40% w/w of COX-2 inhibitor drugs are added and stirred till completely dissolved.
- (b) 0% to 20 % w/w of a Surfactant, as herein described, 0.2% to 60% w/w of a Gelling agent/thickening agent, as herein described, and 0.5% to 60% w/w of one or more Vehicle/Base, as herein described, are mixed in a homogeniser to obtain a homogenised mixture.
- (c) The mixture obtained in step (a) is added to the homogenised mixture obtained in step (b) under stirring without vortex formation to avoid aeration. The mixture is neutralised or its pH adjusted by addition of 0.0% to 5.0% of neutralizing agent or a pH adjusting agent to bring the pH of the product on the acidic side, as herein described, with slow stirring resulting in the preparation of the desired Anti-inflammatory and Analgesic Composition.



As Percutaneous enhancer any chemical can be used which interacts with the stratum comeum layer of the mammalian skin causing reversible change in its barrier properties.

Preferably, as Percutaneous enhancer any known Percutaneous enhancer may be used preferably a C<sub>12-24</sub> mono or poly-unsaturated fatty acids such as vaccenic, cis-vaccenic, Linoleic, Linolenic, elaidic, oleic, petroselinic, erucic or nervonic acid or any of their corresponding alcohols, especially oleic acid or oleyl alcohol or 1-dodecylazacycloheptane-2-one also known as azone; sulphoxides like dimethylsulphoxide, n-decyl methylsulphoxide; Amides like dimethylacetamide, dimethylformamide and N, N-diethylm-tolamide; Pyrrolidones like 2-pyrrolidone and N-methyl-2 Pyrrolidone, volatile oils like oil of citrata, mentha, winter green.

As surfactant, any pharmaceutically acceptable hydrophilic or lipophilic surfactant or mixture thereof may be used, especially suitable for this purpose are the reaction products of natural or hydrogenated vegetable oils and ethylene glycol i.e. polyoxyethylene glycolated natural or hydrogenated vegetable oils, e.g. polyoxyethylene glycolated natural or hydrogenated castor oils; especially various tensides available under the trade name CREMOPHOR particularly CREMOPHOR RH 40 and CREMOPHOR EL. Also suitable for use are the various surfactants available under the trade name NIKKOL e.g. NIKKOL HCO-60.

Polyoxyethylene-Sorbitan fatty acid esters e.g. mono and tri-lauryl, palmityl, stearyl and oleyl esters e.g. those available under the trade name TWEEN preferably TWEEN 40 and TWEEN 80.

Polyoxyethylene-polyoxypropylene block copolymers e.g. especially those available under the trade name POLOXAMER preferably POLOXAMER 188.

Polyoxyethylene fatty acid esters, for example polyoxyethylene stearic acid esters, commercially available under the trade name MYRJ as well as polyoxyethylene fatty acid esters commercially available under the trade name CEIOL HE;

Propylene glycol mono-and di-fatty acid esters such as propylene glycol dicaprylate, propylene glycol dilaurate, propylene glycol hydroxystearate, propylene glycol isostearate, propylene glycol laurate, propylene glycol ricinoleate, propylene glycol stearate;

Examples of suitable lipophilic surfactants include trans-esterification products of natural vegetable oil triglycerides and polyalkylene polyols. Preferred are products obtained by trans-esterification of 2 molar parts of natural vegetable oil triglycerides with one molar part of polyethylene glycol (e.g. having an average molecular weight of from 200 to 800). Various forms of such trans-esterification product are commercially available under the trade name LABRAFIL, preferably LABRAFIL M 1944 CS;

Sorbitan fatty acid esters commercially available under the trade name SPAN including Sorbitan monolauryl, monopalmityl, -monostearyl, -tristearyl-monooleyl and -trioleyl esters;

Monoglycerides e.g. Glycerol monooleate, glycerol monopalmitate and glycerol monostearate commercially available under the trade names MYVATEX, MYVAPIEX and MYVEROL.

As Gelling Agent/Thickening agent, any known such pharmaceutically acceptable agent may be used including synthetic or semi-synthetic polymeric materials, polyacrylate and polyacrylate co-polymeric resins e.g. polyacrylic acid and polyacrylic acid/methacrylic acid resins, commercially available under the trade name CARBOPOL, particularly CARBOPOL 934, 940 and 941 and EUDRAGIT, particularly EUDRAGIT E, L, S, RL, and RS;

Cellulose and cellulose derivatives including alkyl celluloses e.g. methyl-, ethyl-, and propyl-celluloses; hydroxyalkyl-celluloses e.g. hydroxypropyl cellulose, hydroxypropyl alkylcellulose such as hydroxypropyl-methyl-cellulose, acylated celluloses e.g. cellulose-acetates, cellulose acetate phthalates and salts thereof such as sodium carboxymethyl cellulose;

Polyvinyl resins including polyvinylacetates and alcohols as well as other polymeric materials including alginates e.g. alginic acid and salts thereof e.g. sodium alginate and propylene glycol alginate.

As Neutralising/pH adjusting agent any such conventional such agent may be used including sodium bicarbonate, sodium hydroxide, potassium hydroxide, borax, disodium hydrogen phosphate and sodium dihydrogen phosphate. Preferably polar organic amines like diethylamine, diisopropanolamine, triethylamine and triethanolamine may be used, acidifying agents including hydrochloric acid, lactic acid, malic acid, tartaric acid and the like may also be used.

As vehicles/base, the following may be used :

Pharmaceutically acceptably lower (having  $C_{1-5}$ ) alkanols, particularly ethanol; water soluble macrogels like polyethylene glycol having an average molecular weight from 200 to 600; 1, 2-propylene carbonate, propane-1, 2-diol and 1, 2-propylene glycol; glycerol triacetate or (1,2,3,)-triacetin; lower ketones, particularly acetone and 1,2,3 - propanetriol may be incorporated. Water in varying concentration may be added to provide the requisite hydrophilic nature to the composition.

Pharmaceutically acceptable  $C_{1-5}$  alkyl or tetra hydrofurfuryl; di or partial ether of a low molecular weight mono or polyoxy-alkanediol particularly those available under the trade names TRANSCUTOL and GLYCOFUROL.

As the base having lipophilic properties for the preparation of emulsions, fatty acid triglycerides, preferably medium chain fatty acid triglycerides; vegetable oils like coconut oils, olive oil, castor oil and their derivatives; and ethyl oleate may be used.

As base, for the preparation of the said therapeutic composition in the form of an ointment, fatty acids, fats, oils and waxes of animal origin like bees wax, spermacetii, wool fat, waxes of vegetable origin or mineral origin like hard, soft and liquid paraffin may be used.

The topical dosage forms are formulated suitably such that the resultant product is easy to apply and is non-staining.

For the therapeutic composition in form of an aerosol formulation for topical applications, pharmaceutically acceptable propellants may be used such as chlorofluoro carbons e.g. the Propellant 11, Propellant 12, Propellant 114; Hydrocarbon propellants like n-butane, isobutane and propane; compressed gas propellants e.g. Nitrous oxide, carbon dioxide, and nitrogen.

The novel therapeutic composition according to the present invention may be used in the following forms :

1. Topical gel.
2. Oil-in-water or water-in-oil emulsion or micro-emulsion or cream.
3. Solution for topical applications.
4. Ointment.
5. Aerosol formulation for topical applications.

The therapeutic composition according to the present invention may be applied on the skin by utilising a physical form of energy like electrical energy or ultrasonic energy to effect better percutaneous absorption of the drug.

The invention will now be described with reference to the foregoing examples :

### EXAMPLE 1

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#### Preparation of topical gel dosage form

Sl.No.	Component	Quantity
1.	Celecoxib	2.00 g
2.	Dimethylacetamide	22.0 g
3.	Ethyl Alcohol	40.0 g
4.	Acetone	10.0 g
5.	Cremophor RH 40	4.0 g
6.	Propylene glycol	38.0 g
7.	Polyethylene glycol 400	48.8 g
8.	Carbopol 934	4.0 g
9.	Water	30.0 g
10.	Diethylamine	1.2 g
	Total	200.0 g =====

Step (a) Dimethylacetamide is mixed with ethyl alcohol and acetone at 30°C. in a container with stirring. To the mixture obtained Celecoxib is added and stirred till completely dissolved.

Step (b) Propylene glycol, polyethylene glycol 400 and water are mixed in homogenizer. To the homogenised mixture obtained, 1.5% w/w of carbopol 934 is added in small amounts at a time at room temperature and the speed of the homogenizer is kept at approximately 1500 – 2000 rpm.

Step © The mixture obtained in step (a) is added to the mixture obtained in step (b) under stirring without vortex formation to avoid aeration preferably under vacuum (25 mm of Hg). The mixture obtained is neutralised by slow addition of diethylamine with slow stirring at a temperature of 25° - 30°C and under vacuum (25 mm of Hg) to affect gel formation.

## EXAMPLE 2

### Preparation of topical gel dosage form

Sl.No.	Component	Quantity
1.	Rofecoxib	2.00 g
2.	Dimethylacetamide	22.0 g
3.	Ethyl Alcohol	40.0 g
4.	Acetone	10.0 g
5.	Cremophor RH 40	4.0 g
6.	Propylene glycol	38.0 g
7.	Polyethylene glycol 400	48.8 g
8.	Carbopol 934	4.0 g
9.	Water	30.0 g
10.	Diethylamine	1.2 g
	Total	200.0 g

=====

Step (a) Dimethylacetamide is mixed with ethyl alcohol and acetone at 30°C. in a container with stirring. To the mixture obtained Rofecoxib is added and stirred till completely dissolved.

Step (b) Propylene glycol, polyethylene glycol 400 and water are mixed in homogenizer. To the homogenised mixture obtained, 1.5% w/w of carbopol 934 is added in small amounts at a time at room temperature and the speed of the homogenizer is kept at approximately 1500 – 2000 rpm.

Step © The mixture obtained in step (a) is added to the mixture obtained in step (b) under stirring without vortex formation to avoid aeration preferably under vacuum (25 mm of Hg). The mixture obtained is neutralised by slow addition of diethylamine with slow stirring at a temperature of 25° - 30°C and under vacuum (25 mm of Hg) to affect gel formation.

### EXAMPLE 3

#### Preparation of emulsion type topical dosage form

Sl.No.	Component	Quantity
1.	Rofecoxib	1.0 g
2.	Transcutol	35.0 g
3.	Water	10.0 g
4.	Disodium Hydrogen Phosphate	0.1 g
5.	Cremophor RH 40	5.0 g
6.	Labrafil M 1944 CS	10.0 g
7.	Glyceryl monostearate	8.0 g
8.	Stearic acid	13.0 g
9.	Ethyl oleate	2.9 g
10.	Diethyl Sulphoxide	15.0 g
Total		100.0 g
		=====

Dissolve Rofecoxib in a mixture of (6), (7), (8), (9) and (10) with warming. Separately mix (2), (3), (4) and 5 and slowly add the Rofecoxib mixture to it with stirring.



**EXAMPLE 4**Preparation of emulsion type topical dosage form

Sl.No.	Component	Quantity
1.	Celecoxib	1.0 g
2.	Transcutol	35.0 g
3.	Water	10.0 g
4.	Disodium Hydrogen Phosphate	0.1 g
5.	Cremophor RH 40	5.0 g
6.	Labrafil M 1944 CS	10.0 g
7.	Glyceryl monostearate	8.0 g
8.	Stearic acid	13.0 g
9.	Ethyl oleate	2.9 g
10.	Diethyl Sulphoxide	15.0 g
<b>Total</b>		<b>100.0 g</b> =====

Dissolve Celecoxib in a mixture of (6), (7), (8), (9) and (10) with warming. Separately mix (2), (3), (4) and 5 and slowly add the Celecoxib mixture to it with stirring.

**EXAMPLE 5**Preparation of solution type dosage form for topical application

Sl.No.	Component	Quantity
1.	Celecoxib	1.0 g
2.	Dimethyl formamide	10.0 g
3.	Poloxamer 188	2.0 g
4.	Ethyl alcohol	20.0 g
5.	Propylene glycol	25.0 g
6.	Polyethylene glycol 400	42.0 g
7.	Hydroxypropylmethyl cellulose	1.0 g
8.	Triethanolamine	0.2 g
9.	Water	1.0 g
<b>Total</b>		<b>100.0 g</b> =====

Celecoxib is dissolved in (2) with stirring and (3), (4), (5), (6), (7) and (8) are added to obtain a clear solution with stirring.

### EXAMPLE 6

#### Preparation of solution type dosage form for topical application

Sl.No.	Component	Quantity
1.	Rofecoxib	1.0 g
2.	Dimethyl formamide	10.0 g
3.	Poloxamer 188	2.0 g
4.	Ethyl alcohol	20.0 g
5.	Propylene glycol	25.0 g
6.	Polyethylene glycol 400	42.0 g
7.	Hydroxypropylmethyl cellulose	1.0 g
8.	Triethanolamine	0.2 g
9.	Water	1.0 g
Total		100.0 g =====

Rofecoxib is dissolved in (2) with stirring and (3), (4), (5), (6), (7) and (8) are added to obtain a clear solution with stirring.

### EXAMPLE 7

#### Preparation of ointment type dosage form topical application

Sl.No.	Component	Quantity
1.	Rofecoxib	2.0 g
2.	Dimethylsulphoxide	21.0 g
3.	Glycerylmonostearate	16.0 g
4.	Mineral oil	62.0 g
5.	White Petrolatum	97.0 g
6.	Water	2.0 g
Total		200.0 g =====

Warm (3), (4) and (5) and add with stirring a solution of Rofecoxib in dimethyl sulphoxide.

### EXAMPLE 8

Preparation of ointment type dosage form topical application

Sl.No.	Component	Quantity
1.	Celecoxib	2.0 g
2	Dimethylsulphoxide	21.0 g
3.	Glycerylmonostearate	16.0 g
4.	Mineral oil	62.0 g
5.	White Petrolatum	97.0 g
6.	Water	2.0 g
Total		200.0 g

=====

Warm (3), (4) and (5) and add with stirring a solution of Celecoxib in dimethyl sulphoxide.

### EXAMPLE 9

Preparation of an aerosol dosage form for topical use.

Sl.No.	Component	Quantity
1.	Celecoxib	1.0 g
2.	Dimethylacetamide	10.0 g
3.	Ethyl alcohol	10.0 g
4.	Cremophor RH 40	10.0 g
5.	Propellant 114	29.0 g
6.	Propellant 12	39.0 g
7.	Water	1.0 g
Total		100.0 g

=====

**EXAMPLE 10**Preparation of an aerosol dosage form for topical use.

Sl.No.	Component	Quantity
1.	Rofecoxib	1.0 g
2.	Dimethylacetamide	10.0 g
3.	Ethyl alcohol	10.0 g
4.	Cremophor RH 40	10.0 g
5.	Propellant 114	29.0 g
6.	Propellant 12	39.0 g
7.	Water	1.0 g
Total		100.0 g =====

**EXAMPLE 11**Preparation of an aerosol dosage form.

Sl.No.	Component	Quantity
1.	Celecoxib	1%
2.	Methyl Salicylate	20%
3.	Eucalyptus	6%
4.	Clove oil	1%
5.	Menthol	4%
6.	Camphor	10%
7.	Cinnamon oil	0.5%
8.	Terpentine oil	10%
9.	Solvent	q.s to 100%

**EXAMPLE 12**

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Preparation of an aerosol dosage form.

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Sl.No.	Component	Quantity
<hr/>		
1.	Rofecoxib	1%
2.	Methyl Salicylate	20%
3.	Eucalyptus	6%
4.	Clove oil	1%
5.	Menthol	4%
6.	Camphor	10%
7.	Cinnamon oil	0.5%
8.	Terpentine oil	10%
9.	Solvent	q.s to 100%

**EXAMPLE 13**

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**Topical Preparation**

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1.	Purified Water	q.s. 100 g
2.	Glycerin	3.00 g
3.	Cetostearyl alcohol	5.00 g
4.	Cetyl alcohol	2.00 g
5.	Oil of wintergreen	2.00 g
6.	Caprylic and capric triglyceride	1.80 g
7.	Rofecoxib	0.5 g
8.	Citrata oil	3.0 g
9.	Parabens	1.0 g
10.	Tocopherol-Ascorbyl palmitate soy lecithin	0.01 g
11.	Citric acid	0.02 g

**Process:**

- Step 1. Mix 1 and 2 in a jacketted vessel.  
Step 2. Mix ingredients 3 to 11 separately at 40 – 60°C  
Step 3. Mix phases of step 1 and 2 using a homogenizer

**EXAMPLE 14**

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**Topical Preparation**

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1.	Purified Water	q.s. 100 g
2.	Glycerin	3.00 g
3.	Cetostearyl alcohol	5.00 g
4.	Cetyl alcohol	2.00 g
5.	Oil of wintergreen	2.00 g
6.	Caprylic and capric triglyceride	1.80 g
7.	Celecoxib	0.5 g
8.	Citrata oil	3.0 g
9.	Parabens	1.0 g
10.	Tocopherol-Ascorbyl palmitate soy lecithin	0.01 g
11.	Citric acid	0.02 g

**Process:**

- Step 1. Mix 1 and 2 in a jacketted vessel.  
Step 2. Mix ingredients 3 to 11 separately at 40 – 60°C  
Step 3. Mix phases of step 1 and 2 using a homogenizer

Since many apparently different embodiments of the present invention could be made without departing from the spirit and scope thereof, it is intended that the description of the invention herein be interpreted as being illustrative only and not limiting in any manner whatsoever.

**We Claim :**

1. A therapeutic anti- inflammatory and analgesic pharmaceutical composition for topical /transdermal use which comprises :  
Selective COX-2 inhibitor drugs from 0.1% to 40% w/w and  
Percutaneous absorption enhancing vehicle/base from 60% to 99.9% w/w
2. A composition as claimed in claim 1 wherein said percutaneous absorption enhancing vehicle/base comprises:-  
  
Percutaneous enhancer from 0.5% to 60% w/w and  
Vehicle/base from 2.0% to 98%
3. A composition as claimed in claim 1 or 2 further comprising 0% to 60% w/w of the gelling agent/ thickening agent.
4. A composition as claimed in claim 1 or 2 further comprising 0% to 20% w/w of a surfactant.
5. A composition as claimed in claim 1 or 2 further comprising a neutralizing agent/pH adjusting agent in an amount 0 to 5% w/w.
6. A composition as claimed in claim 1 or 2 wherein the percutaneous enhancer is selected from the group which interacts with stratum comeum layer of the mammalian skin causing reversible change in its barrier properties.

7. A composition as claimed in claim 1 or 2 wherein the percutaneous enhancer is selected from sulphoxides, amides or pyrrolidones, laurocapram essential oils, or C<sub>12-24</sub> mono or poly-unsaturated fatty acids or any of their corresponding alcohols.
8. A composition as claimed in claim 7 wherein the percutaneous enhancer is dimethylacetamide.
9. A composition as claimed in claim 4 wherein the surfactant is a pharmaceutically acceptable hydrophilic or lipophilic surfactant or mixture thereof.
10. A composition as claimed in claim 9 wherein the surfactant is selected from polyoxyethylene glycolated natural or hydrogenated castor oil, polyoxyethylene-sorbitan fatty acid esters, polyoxyethylene-polyoxypropylene block copolymers, polyoxyethylene fatty acids esters, propylene glycol mono-and di-fatty acid esters; lipophilic surfactants like sorbitan fatty acid esters, monoglycerides, sugar esters, transesterification products of natural vegetable oil triglycerides and alkylene polyols.
11. A composition as claimed in claim 3 wherein said gelling/thickening agent is selected from natural, synthetic or semi-synthetic polymeric materials, like polyacrylate and polyacrylate co-polymeric resins, cellulose and cellulose derivatives or polyvinyl resins.



12. A composition as claimed in claim 5 wherein the neutralizing/pH adjusting agent is selected from the group comprising sodium bicarbonate, sodium hydroxide, potassium hydroxide, borax, disodium hydrogen phosphate, sodium dihydrogen phosphate, hydrochloric acid, Lactic acid, phosphoric acid and malic acid.
13. A composition as claimed in claim 5 wherein neutralizing/pH adjusting agent is a polar organic amine.
14. A composition as claimed in claim 2 wherein the vehicle/base is selected from pharmaceutically acceptably lower ( $C_{1-6}$ ) alkanols; water soluble macrogols; 1,2-propylene carbonate, Butylene glycol, polypropylene glycol, 1-2-propylene glycol, glycerol triacetate, glycerol, lower ketones, chlorofluorocarbons, hydrofluorocarbons, and water.
15. A therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/ transdermal use which comprises :

Selective COX-2 inhibitor drugs: 0.1% to 40% w/w

Percutaneous enhancer : 0.5% to 60% w/w,

Gelling agent/thickening agent : 0% to 60% w/w,

Vehicle/base : 2% to 98% w/w

and 0 to 20% w/w of surfactant.

16. A therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/ transdermal use which comprises :  
Selective COX-2 inhibitor drugs : 0.1% to 40% w/w.  
Percutaneous enhancer : 0.5% to 60% w/w.  
Gelling agent/thickening agent : 0% to 60% w/w.  
Vehicle/base : 2% to 98% w/w  
and 0 to 20% w/w of surfactant, and 0 to 5% w/w of neutralizing/pH adjusting agent.
17. A composition as claimed in claim 1 wherein the Selective COX-2 inhibitor drugs are selective from the group comprising Celecoxib and Rofecoxib.
18. A process for the manufacture of a therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/transdermal use which comprises mixing together in any convention manor 0.1% to 40% w/w of Selective COX-2 inhibitor drugs with 60% to 99.9% W/W of percutaneous absorbiton enhancing vehicle/base under ambient conditions.
19. A process for the manufacture of a therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/transdermal use as claimed in claim 18 wherein the said percutaneous absorbiton enhancing vehicle/base comprises percutaneous enhancer from 0.5% to 60% w/w and vehicle/base from 2.0% to 98%

20. A process for the manufacture of a therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/transdermal use as claimed in claim 18 or 19 further comprising 0% to 60% w/w of the gelling agent/thickening agent.
21. A process for the manufacture of a therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/transdermal use as claimed in claim 18 or 19 further comprising 0% to 20% w/w of a surfactant.
22. A process for the production of a therapeutic and analgesic pharmaceutical composition for topical/transdermal use as claimed in any of the preceding claims 18 or 19 which comprises :
- (a) mixing 0.5% w/w to 60% w/w of a percutaneous enhancer with 2% to 98% w/w of one or more vehicles or bases ;
  - (b) adding to the mixture of step (a) 0.1% w/w to 40% w/w of Selective COX-2 inhibitor followed by stirring the mixture until completely dissolved ;
  - (c) mixing separately 0% w/w to 20% w/w of a surfactant, 0% w/w to 60% of a gelling agent/ thickening agent and 2.0% w/w to 98% w/w of one or more vehicles or bases and mixing the entire mixture; and
  - (d) adding the mixture obtained in step (b) to the mixture obtained in step (c) under stirring to obtain the composition.

23. A process as claimed in claim 22 wherein a neutralizing agent or a pH adjusting agent is added to the composition in step (d) to neutralize or adjust the pH of the mixture.
24. A process as claimed in claim 23 wherein the said neutralizing agent/pH adjusting agent is added in an amount of up to 5.0% w/w.
25. A therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/transdermal use substantially as herein described with reference to the foregoing description and the accompanying examples.
26. A process for the production of therapeutic anti-inflammatory and analgesic pharmaceutical composition for topical/transdermal use substantially as herein described with reference to the foregoing description and the accompanying examples.

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ning of each regular issue of the PCT Gazette.

(54) Title: THERAPEUTIC ANTI-INFLAMMATORY AND ANALGESIC COMPOSITION CONTAINING SELECTIVE COX-2  
INHIBITORS

(57) Abstract: A therapeutic anti-inflammatory and analgesic composition for topical/transdermal use which comprises: Selective  
Cox-2 inhibitor drugs from 0.1% to 40% w/w and percutaneous absorption enhancing vehicle/base from 60% to 99.9% w/w. Op-  
tionally Gelling agent/thickening agent (0% to 60% w/w) surfactant (0% to 20% w/w). Neutralizing agent/pH adjusting agent (0%  
to 5% w/w) may be added to the said composition.

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# INTERNATIONAL SEARCH REPORT

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## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K47/12 A61K47/10 A61K47/22 A61K47/18 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, MEDLINE, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 812 587 A (PANACEA BIOTEC LTD) 17 December 1997 (1997-12-17) the whole document	1-16, 18-26
X	EP 0 782 855 A (HELSINN HEALTHCARE SA) 9 July 1997 (1997-07-09)  the whole document	1-7,9, 11, 13-16, 18,25,26

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

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# INTERNATIONAL SEARCH REPORT

International Application No

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## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 92 04019 A (BEECHAM GROUP PLC) 19 March 1992 (1992-03-19)</p> <p>page 1, line 1 - line 17 page 2, line 7 - line 34 page 4, line 6 -page 8, line 10 page 12, line 26 - last line; claims; examples 1-3</p>	<p>1-4,6,7, 9-11,14, 15, 18-21, 25,26</p>
X	<p>WO 00 00120 A (PRAECIS PHARM INC ;WILLIAMS C DONALD (US); MURDOCK ROBERT W (US)) 6 January 2000 (2000-01-06)</p> <p>claims 1,2,9,16-18,28-30,34,48-50; example 73 page 4, line 14 - line 18 page 5, line 12 - last line page 10, line 12 - line 31 page 11, line 27 -page 12, line 23 page 13, line 35 -page 14, line 10</p>	<p>1-4,6, 10,11, 15, 17-21, 25,26</p>
X	<p>EP 0 147 146 A (AMERICAN HOME PROD) 3 July 1985 (1985-07-03)</p> <p>page 3, line 7 - last line page 4, line 33 -page 5, last line; claims 1-4,7,8; example 3</p>	<p>1,2,6, 18,19, 25,26</p>
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CRYER B ET AL: "The advent of highly selective inhibitors of cyclooxygenase-a review - Implications for gastrointestinal toxicity"</p> <p>PROSTAGLANDINS AND OTHER LIPID MEDIATORS, BUTTERWORTH, STONEHAM, MA, US, vol. 56, no. 5-6, August 1998 (1998-08), pages 341-361, XP004156755</p> <p>ISSN: 0090-6980</p> <p>page 342, line 14 - line 34; table 1</p> <p>page 351, line 21 -page 353, last line; table 3</p> <p>----</p>	1-26
A	<p>DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1995</p> <p>SPANGLER R S: "New insight into NSAID-induced gastropathy."</p> <p>Database accession no. PREV199698736774</p> <p>XP002176551</p> <p>abstract</p> <p>&amp; INFLAMMOPHARMACOLOGY, vol. 3, no. 4, 1995, pages 347-350, ISSN: 0925-4692</p> <p>-----</p>	1-26



## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Present claims 1-24 relate to a product or method defined by reference to a desirable characteristic or property, namely selective COX-2 inhibitor drugs. The term "selective COX-2 inhibitor drugs" defines the active agent by the selectivity of its enzyme inhibition. However, a compound cannot be sufficiently characterised by the selectivity of its enzyme inhibition as it is done by an expression like "selective COX-2 inhibitor drugs", because it is impossible to know which substances are encompassed in this expression.

The claims cover all products or methods having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products/compounds/methods/apparatus. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the products or methods by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products or methods mentioned in claim 17, examples 1-14, and the concept of selective COX-2 inhibitor drugs.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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information on patent family members

International Application No

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